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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,773	03/22/2002	Arnold Hilgers	Q67842	1749

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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary	Application No.	Applicant(s)
	10/018,773	HILGERS, ARNOLD
	Examiner	Art Unit
	Dave T Nguyen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *22 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claims 1-60 have been canceled, claims 61-100 have been added by the amendment filed September 19, 2003.

Claims 61-100 are pending for examination.

Claim 74 is objected because the phase "a carbohydrate-based polymers or derivatives thereof" is grammatically incorrect. A change to -- a carbohydrate-based polymer or derivative thereof -- is suggested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 61-100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1/ A method for the preparation of microparticles from a liquid on-phase system containing biological material and a suitable amount of at least two compounds being incompatible in aqueous solution, the method consisting of the method step of evaporating water from the one-phase system leading to a phase separation with a dispersed phase and a continuous phase, thereby producing the formation of the microparticles, wherein the first compound of the at least two compounds is a dextran-based polymer, and the second compound of the at least two compounds is a polyaliphatic alcohol or derivative thereof, and wherein the evaporating step does not employ any emulsification mean, vortexing step, and stirring step.

2/ A composition comprising microparticles produced by the method of 1/,

does not reasonably provide enablement for any other microparticle produced simply by the step of evaporation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As summarized by applicants on page 8 of the response, the main thrust of the claimed invention as now amended is drawn to a method for the preparation of microparticles from a liquid one-phase system by initializing the phase separation by evaporation of water. As such, Applicant claims that the formation of a dispersion (*i.e.,* the microparticles) can be done by the evaporation of water only, and no conventional phase separation method or other emulsification means like stirring or vortexing is needed, *e.g.,* also see the specification, page 11 and page 17. As such, the claimed methods and compositions produced by the claimed method do not embrace any steps and/or emulsification means/materials other than active step(s) of evaporating water from a liquid one-phase system.

The state of the prior art, as evidenced by the specification on page 9, clearly indicates that evaporation of water alone is not sufficient to induce formation of microparticles as the result of the presence of any two chosen polymers present in a liquid one phase-system. While the specification and the state of the prior art appear to acknowledge that is well-accepted within the scientific community that under certain conditions, an aqueous polymer solution will spontaneously separate into a two phase polymer system, thereby leading to the formation of microparticles, the state of the prior art clearly teaches that without the use of emulsification means, *e.g.,* chemical compound/polymer, pH, mixing and/or vortexing, the step of evaporating water alone is not sufficient to induce the formation of microparticles from any chosen two polymers present in a liquid one phase-system, *e.g.,* see page 9 of the specification, and entire column 6 and the last paragraph of column 8 of US Pat No. 6,528,035 (Mathiowitz); column 12, 4th par., US Pat No. 6,224,894 B1; and lines 47-61 of column 6, US Pat No. 5,609,886. However, applicant in this present application contemplates that on the contrary of the teaching and/or guidance provided by the state of the prior art, the formation of microparticles as the result of the present of any two polymers present in a liquid one phase system, regardless of their respective pH, ionic composition, and/or the molecular weight and concentration of each of the respective polymers, can be produced by simply performing the step of evaporating water from the system. In order to support the contemplation, Applicant provides working examples showing the formation of microparticles by simply performing the step of evaporating water from one–phase aqueous solutions containing dextran (a carbohydrate based polymer) and PEG, or PVP or Tween-80, or pluronic F-68, or

Ficoll. By showing the successful formation of dextran-based microparticles, applicant then claims that this singly evaporation based process can be reasonably extrapolated the formation of microparticles by any other polymer(s), wherein only the single step of evaporating water from a liquid one phase system is carried out to effect the formation of microparticles. In fact, the claims also embrace a scenario by having any liquid one phase system composed of any two aqueous incompatible polymers sitting at the temperature of 0°C or pressure at 0.1 mm Hg p. However, a skilled artisan on the basis of the guidance and teachings provided by the state of the prior art, would not have reasonably believed that applicant's claimed process can be applied uniformly to any two polymers other than the use of a dextran-based polymer and a polyaliphatic alcohol. The showing of one single species of Dextran, and PEG, PVP, Tween-80, Pluronic F-68 or Ficoll is not sufficient to overcome many teachings in the prior arts, which uniformly teach that without the use of emulsification means, *e.g.,* chemical compound/polymer, pH, mixing and/or vortexing, the step of evaporating water alone is not sufficient to induce the formation of microparticles from any chosen two polymers present in a liquid one phase-system, *e.g.,* see page 9 of the specification, and entire column 6 and the last paragraph of column 8 of US Pat No. 6,528,035 (Mathiowitz). As such, it is not apparent how a skilled artisan, without any undue experimentation, practices the full breadth of the claimed invention at the time the invention was made.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 61-100 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 61-100 are indefinite because the claim language of the base claims, when given the customary and ordinary meaning given in the prior art, and when read as a whole in light of the as-filed specification, is not limited *per se* to applicant's own interpretation of the claimed invention as set forth in the latest response, which clearly indicates that the claimed invention and/or the evaporation step does

not embrace the active steps of employing emulsification means and/or mechanical means of vortexing/stirring. However, no where in the specification, applicant at the time the invention provides any written support to support applicant's latest interpretation of a much narrower meaning of "evaporation", which is at best a functional limitation characterizing a conversion of a liquid form into vapors. While the specification appears to provide a written support for the embodiment as now presented by applicant, the claims as presently pending do not reflect *per se* applicant's interpretation of the scope of the claimed invention. As such, the claims are not definite because a) the metes and bounds of the claims are not clearly defined by the as-filed application; and b) the claim language do not reflect applicant's later interpretation, which states that 1/ only an active step of evaporation water is carried out for a liquid one phase system as claimed; and 2/ that the "evaporation" step excludes any steps of employing emulsification means and/or vortexing and mixing the polymeric compounds present in the liquid one phase system.

In view of the reasons set forth in the immediately preceding paragraph, and in view of the fact that claims *per se* are not necessarily limited to only applicant's later interpretation of the claim language present in the amended claims, the previous prior art rejections remain applicable.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 61-100 are rejected under 35 USC 102 (b) as being anticipated by any of Woiszvillo (US Pat No. 5,849,884), OctoPlus (EP 0 842 657), or Magnus (EP 0 213 303).

The claimed language as recited in the claims embrace a method for the preparation of microparticles from a liquid on-phase system containing biological material and a suitable amount of at least two compounds being incompatible in aqueous solution, the method comprising the method step of evaporating water from the one-phase system leading to a phase separation with a dispersed phase and a continuous phase, thereby producing the formation of the microparticles, wherein the first compound of the at least two compounds is a dextran-based polymer, and the second compound of the at least two compounds is a polyaliphatic alcohol or derivative thereof, and wherein the method may include any emulsification mean, vortexing step, and stirring step in addition to the evaporation step.

The claims also claim a composition comprising microparticles produced by the claimed methods, wherein the limitation of "composed of at least 75% of said polymer compounds and 25% or less of said biological material in said aqueous solution" only can be characterized or made meaningful when the composition are interpreted as product by process claims. The fact that 75% of polymers used as starting materials in Applicant's claimed method are now in the microparticle forms of the claimed compositions does not necessarily particularly point out as to what is exactly the final concentration or weight of the polymer or microparticle relative to that of the biological material present physically in the claimed compositions. Thus, to the extent that the total weight of the claimed composition are not limited in any way to any concentration and/or weight of either the microparticle or biological material, the newly added limitation does not carry any patentable weight for the claimed compositions. As such, the prior art rejections remain applicable as stated here below:

> With respect to the method and composition claimed as set forth in the immediately preceding paragraphs, Woiszvillo teaches the same on column 3, line 21 –column 4, line 5, examples). OctoPlus teaches the same on pages 3-5. Particularly, OctoPlus teaches on page 4, lines 39-41, that suitable emulsifiers are copolymers, preferably block-copolymers, of units of the two incompatible polymers, e.g., a block-copolymer of PEG and Dextran, used to create the two-phase system. Magnus also teaches the same throughout the disclosure, particularly pages 2-4, 5-6, and 12. With respect to Woiszvillo: column 3 discloses that the polymers are carbohydrate based polymers, dextran or a polymer mixture of polyminylpyrrolidone and polyethylene glycol (PEG); The MW of PEG is disclosed on column 12; Example 5, column 19 discloses that polylysine is employed as a nucleic acid binding agent; Column 10 discloses that surfactant composed of any known phospholipid can be employed for

attachment to the surface of the formed microparticles; and MW of Dextran is disclosed on column 22. With respect to Magnus, Magnus teaches that PEG and dextran can be used in a two-phase system, wherein MW of both are also disclosed, page 5; page 3 discloses that one way to achieve removal of water from the dispersed phase comprises the application of methods such as evaporation; Page 12 of Magnus also discloses that particles can be produced without heating, if the dispersed phase is dehydrated with a watermiscible solvent

The functional limitations of an occurrence of a spontaneous formation of the dispersed phase, and of the percent relative to that used as starting materials in Applicant's claimed process do not carry any patentable weight, since the office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. In the absence of factual evidence to the contrary, the burden is upon the applicant to prove that the claimed products are **functionally different** than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips,* 28 USPQ 1302, 1303 (BPAI 1993), *In re Best,* 562, F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray,* 10 USPQ2d 1922, 1923 (BPAI 1989). Again, the claiming of a new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977); *In re Spada,* 15 USPQ2d 1655, Federal Circuit, 1990. See also MPEP § 2112.01 with regard to inherency and product-by-process claims.

Furthermore, the skill of a person skilled in the art of making microparticles is relatively high, as evidenced by the totality of the prior art of record, and as such, it is well-recognized in the prior art that aqueous solutions of two incompatible polymers will spontaneously separate into a dispersed and continuous phase when a critical polymer concentration has been reached, *e.g.,* evaporation of water. In fact, Woiszvillo teaches on column 12, last paragraph, that "the microparticles may be formed at lower temperatures by utilizing a higher macromolecule concentration". On the other hand, when two incompatible polymers are mixed in such a way that the concentration in the final mixture is already above the critical concentration (see column 7, especially lines 32-40), mechanical energy (e.g., vortexing, stirring) should be put in the system in order to get a finely dispersed phase. Note also that although Woiszvillo teaches the use of conventional emulsification means, like stirring, vortexing and

sonication, evaporation must be necessarily present in the energy added steps, particularly in view of the presence of the added energy as the result of the use of emulsification means, like stirring, vortexing and sonication. As such, a spontaneous formation of a dispersed phase is not excluded. Furthermore, the formation of microparticles can also be observed just by heating one-phase aqueous solutions of incompatible polymers, *e.g.,* example 14.

Thus, the claims are anticipated by the cited references.

Note also that it is well recognized by a person of ordinary skill in the art, as evidenced by the totality of the prior art of record, that a dispersed phase would form when a critical polymer concentration has been reached, and that it is within the purview of those of ordinary skill in the art of making microparticles to employ any concentration step such as evaporation without heating in order to achieve the critical polymer concentration required for the formation of a dispersed phase in a two-phase system comprising to incompatible polymers such as dextran and PEG, and a biologically active material such as a nucleic acid molecule.

Applicant's response (pages 9-12) has been considered by the examiner but is not found persuasive because of the reasons set forth above. More specifically, applicant's attempt to narrow the meaning of the claim language as recited in the presently pending claims is simply an opinion. As such, the methods employed in the prior art remain embraced by the presently pending claims. Insofar as the composition claims are concerned, the newly added limitation regarding the percent of the microparticle and/or biological material relative to that of the starting materials employed in applicant's claimed process, the limitations can only be characterized as product by process claims, and thus, do not carry any patentable weight in the claimed compositions. As such, the claimed percent is all relative in meanings, and thus, the prior art rejections remain applicable.

Claims 72-100 are rejected under 35 USC 103(a) as being unpatentable over OctoPlus (EP 0 842 657), or Magnus (EP 0 213 303), each of which taken with Carli (US Pat No. 6,355,273), Mathiowitz (US Pat No. 6,745,779 B2), Burke (US Pat No. 6,183,781) or Gombotz (US Pat No. 6,274,175).

The rejections of the claimed composition as being anticipated by OctoPlus (EP 0 842 657), or Magnus (EP 0 213 303) remain applicable as indicated above. To the extent that the claimed composition embrace a particular weight of microparticle and biological material present in the composition, the claims are also obvious under 35 USC 103:

More specifically, Carli (US Pat No. 6,355,273), Mathiowitz (US Pat No. 6,745,779 B2), Burke (US Pat No. 6,183,781) or Gombotz (US Pat No. 6,274,175) all teach that it is well accepted within the scientific community to employ any percent weight of the microparticle and biological material for the delivery of the biological material to a target tissue or cell. For example, Carli teaches on column 10 that the obtained microparticles has 92.15% by weight of the product, and the drug (nicardipine) has 22.5% by weight of the formed product. Mathiowitz teaches and claim on column 16 that the weight of the biological material of DNA, which can be formulated or loaded into the polymeric microparticle, is about 0.1-90%. Burke teaches on column 14 that formulated microparticles can contain a peptide as the biological material in an amount from at least 0.1 preferably 0.5 to 20% by weight relative to the (co)-polymer matrix, preferably 2.0 to 10, especially 3 to 6% of weight. Gombotz teaches on column 9 that the range of loading of the GM-CSF as the biological material to be delivered is typically between about 0.001% and 10 %, by weight....In a preferred embodiment, GM-CSF is incorporated into PLGA blends to 2% by weight.

Thus, it would have been obvious for a skilled artisan as a matter of design choice to incorporate and/or modify the percent weight of the microparticles and biological material in the methods employed in the primary references, depending on a particular nature of usage of the delivered biological material. One of ordinary skill in the art would have been motivated to do so because the cited prior art teaches that the percent weight of microparticles and biological materials can be routinely modified and because Carli, Mathiowitz, Burke, and Gombotz all teach that it is well accepted within the scientific community to employ any percent weight of the microparticle and biological material for the delivery of the biological material to a target tissue or cell.

Thus, the claimed invention as a whole, was *prima facie* obvious.

The following references are cited to further show that it is well recognized by a person of ordinary skill in the art that a dispersed phase would form when a critical polymer concentration has been reached, and that it is within the purview of those of ordinary skill in the art of making microparticles to employ any concentration step such as evaporation without heating in order to achieve the critical polymer concentration required for the formation of a dispersed phase in a two-phase system comprising to incompatible polymers such as dextran and PEG: Orly, US Pat No. 5,672,301, Gibson, US 6,291,013, Hennink, US 6,303,148 and US 6,395,302.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024.**

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Please note that the examiner is expected to move to a new US PTO office building located in Alexandria on January 12, 2004. The examiner office phone number at the new building is **571-272-0731.**

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER